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Olfactory Function in Latino Farmworkers: Subclinical Neurological Effects of Pesticide Exposure in a Vulnerable Population

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Abstract

Objectives—We compared olfactory function in pesticide-exposed Latino farmworkers and non-farmworkers to explore its use as a subclinical indicator of neurological pesticide effects.

Methods—We recruited 304 current farmworkers and 247 non-farmworkers. All completed odor identification (14 odors) and threshold tests (16 concentrations of n-butanol) using a well-established methodology.

Results—Farmworkers reported significantly greater lifetime pesticide exposure. Performance on both olfactory tests declined with age. Odor identification performance did not differ between groups. For odor threshold, farmworkers needed significantly higher concentrations to detect the odor. Results were unchanged when adjusted for sex, age, and smoking.

Conclusions—Olfactory function differences between farmworkers and non-farmworkers suggest possible neurological effects. Because declining olfactory function is an early symptom of Parkinson's disease and related conditions, it is a possible subclinical indicator of neurodegenerative disease in this vulnerable worker population.

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Keywords

Neurotoxin; pesticide; community-based participatory research; occupational health; vulnerable population; environmental justice; Parkinson's Disease

Introduction

Exposure to pesticides is associated with long term neurodegenerative outcomes, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS).^{1,2} Such associations have been found in several cohort studies of adults occupationally exposed to pesticides over the lifetime.³⁻⁵

Migrant farmworkers in contemporary US agriculture are routinely exposed to a wide variety of pesticides.⁶⁻⁸ These include classes of pesticides such as organophosphorus, organochlorine, and pyrethroid insecticides that are neurotoxins. While some workers may be exposed to large doses on discrete occasions through spills or during application, the more common exposure is long term, low dose exposure to dislodgeable pesticide residues on plants and tools, in soil, and on surfaces at the worksite, as well as "take-home" pesticides tracked into vehicles and housing.⁹⁻¹¹ Documenting any long term outcomes of pesticide exposure among migrant farmworkers is difficult because workers cannot be readily followed over time to determine exposures and vital status.¹² Furthermore, workers frequently are unaware of their pesticide exposure and lack access to information on the types of pesticides used where they work and live.¹³

Because disease endpoints such as Parkinson's disease are unlikely in a healthy worker population, this study attempted to seek associations of subclinical neurological effects with pesticide exposure. Although the study of subclinical measures has become standard for other diseases with an extended period of development (e.g., cardiovascular disease¹⁴), research to investigate possible subclinical neurological effects of pesticides in apparently healthy individuals is limited. If such associations exist, they would suggest that pesticide effects can be detected long before disease endpoints, providing an opportunity to intervene with workers at risk. Olfactory function is impaired early in the disease process for Parkinson's disease and other neurodegenerative diseases.¹⁵ Such neurodegenerative diseases develop over the course of decades, and some epidemiological associations have been demonstrated with exposure to pesticides.¹⁻⁴ The olfactory nerve endings in the nasal mucosa are highly vulnerable to pesticides, either as volatile elements or spray, as substances dissolved in nasal or oral fluids due to contact of contaminated food or hands with the face, or simply due to pesticides in blood flow because the nasal mucosa has such a high vascularity compared to other tissues. Therefore, this study focused on evaluating the association of olfactory function, as a subclinical neurological marker, with pesticide exposure.

We use a study of migrant farmworkers—a population known to experience pesticide exposure at work and live in environments where pesticides are endemic—to investigate possible subclinical neurological effects of exposure. We focus on olfactory function, as this

neurological system is known to be affected early in the disease process of several neurodegenerative diseases.

The goal of this paper is to compare olfactory function in a sample of Latino migrant farmworkers with that of a comparable sample of Latino immigrant workers with no recent history of occupational exposure to pesticides. We focus on two types of olfactory function: the ability to differentiate and identify common odors (odor identification), and the concentration at which an odor can be detected (odor threshold). Specifically, we compare odor identification and odor threshold in current farmworkers and non-farmworkers with significant group differences in lifetime pesticide exposure, adjusting for age, gender, and smoking status.

Methods

Data were collected by the PACE4 project (R01 ES008739) and PEARL project (R21 ES019720) in 2012. These are community-based participatory research (CBPR) studies with Latino communities to examine pesticides exposure and subclinical neurological outcomes (PACE4) and age-related changes in neurological function (PEARL). Both studies compare Latino farmworkers with Latino non-farmworkers selected for minimal occupational pesticide exposure. The protocol was approved by the Wake Forest School of Medicine Institutional Review Board. All participants gave signed informed consent.

Study Sites

Participants were recruited in two areas of North Carolina. Farmworkers were recruited in east central North Carolina. Non-farmworkers were recruited from Forsyth County in the west central region of the state. Although agriculture is practiced in both locales, Forsyth County is largely urban, and agriculture is far more extensive in the east central region.

Sample

Participants were men and women aged 18 to 70 years. All self-identified as Latino or Hispanic and almost all most spoke Spanish as their primary language. Because PACE4 recruited a larger sample restricted only to males, the combined sample reported here is largely male. Farmworkers recruited had to be currently employed as farmworkers and had to have worked in agriculture for at least three years. Non-farmworkers could not have been employed for the past 3 years in jobs that routinely expose workers to pesticides, including farm work, forestry, landscaping, grounds keeping, lawn maintenance, and pest control.

Recruitment was accomplished with the assistance of community partners. Staff of community partner NC Farmworkers Project approached the farmworker camps that they served. They explained the project to the residents of each camp, including the inclusion and exclusion criteria, time commitments and incentives, and asked for volunteers. Volunteers were screened to ensure that they met the inclusion criteria. Project staff worked with Forsyth County community partner El Buen Pastor Latino Community Services and other community organizations to identify and contact potential participants. Project staff explained the project, including the inclusion and exclusion criteria, time commitments and

incentives, and asked if the individual wanted to volunteer. Volunteers were screened to ensure that they met the inclusion criteria.

A total of 304 farmworkers and 247 non-farmworkers were enrolled and completed olfactory testing. Participation rates are difficult to calculate for farmworkers. Because of the communal living and working situation, groups of farmworkers were asked to volunteer. Only the number who agreed to volunteer is available; generally, all of the farmworkers in a camp who met the inclusion criteria volunteered. Farmworkers who did not want to participate could have avoided contact with the project staff or indicated that they did not meet the inclusion criteria to avoid refusing. Among the non-farmworkers, 101 individuals were contacted who did not meet the inclusion criteria. Of those contacted and meeting the inclusion criteria, 87 individuals refused to participate for a participation rate of 77.7% (304/(87+304)). Reasons given for refusing included the time commitment and length of the overall studies (51), reluctance to undergo blood draws (27), need to come to a clinic for data collection (31), and providing contact information (30). Individuals could give more than one reason for refusing.

Data Collection

Farmworker participants completed data collection from May through September, and non-farmworkers completed data collection from June through October. Participants completed an initial questionnaire, generally in the camp (farmworkers) or home or location such as a community center (non-farmworkers), and then attended a clinic at a central location on a Sunday for collection of clinical measures, including olfactory testing. The questionnaire contained demographic and health items, items used to construct measures of lifetime pesticide exposure, and items detailing recent residential exposure for all participants. The questionnaire was developed in English and translated into Spanish. When possible, existing Spanish items were used. The Spanish and English versions were checked for comparable meaning for each item, and item wording was adjusted as needed. The Spanish version of the questionnaire was pre-tested with several native Spanish speakers, and final corrections were made. Interviewers included native Spanish speakers who completed training that addressed questionnaire content and proper technique for conducting interviews.

Two olfactory tests: odor identification and odor detection threshold, were conducted at the clinic in private clinic examination rooms by trained data collectors fluent in Spanish. The two tests were separated in time during the study data collection to avoid issues with participant fatigue. Both tests used customized “Sniffin’ Sticks” kits¹⁶ (Burghart GmbH, Wedel, Germany) developed specifically for this study and population. For odor identification, participants were presented with 14 different odors in a pen-like device and asked to identify them. Odors were chosen in consultation with Dr. Pamela Dalton, Monell Chemical Senses Center, after a pre-test with Latino immigrant workers. Criteria for odor inclusion were that all the odors in the test were likely familiar to participants, odors would be similar in intensity and hedonic tone, and odors were identified by at least 75% of healthy subjects in other studies. Before presenting the odors, the test administrator showed the participant an 11' × 17' poster with color photos representing the odors to be used to assure recognition of the pictures. The test administrator read a list of odors, and asked the

participant if he or she was familiar with that odor and to point to the picture on the poster that represented it. Odors were then presented in an established order by un-capping the odor pen and holding it under the nose of the participant. For each odor presented, participants were shown an 8.5 × 11 page printed with 4 different color photos taken from the poster, one representing the correct answer and three others chosen at random from the other odors in the test battery; the participant was asked to identify the picture corresponding to the odor. Odor detection threshold was assessed using the staircase method with n-butanol, a standard olfactory test odorant used in clinics and field settings worldwide.¹⁷ Sixteen concentrations of the odor were presented one at a time from weakest to strongest dilution in a set randomly ordered with two blanks. Participants were asked to close their eyes during the test. For each set of three odor pens, the test administrator uncapped each pen and held it under the participant's nose; after all three had been presented, the participant was asked which of the three held the odor. Administration continued in an ascending staircase, forced-choice presentation until the participant could distinguish the chemical from the blanks for three consecutive presentations. The odor threshold test was administered three times.

Olfactory test data collectors underwent extensive training, followed by practice sessions to attain proper timing and dexterity with manipulating the odor pens. Prior to data collection, each was required to complete administration observed by the first author to assure proper technique and data recording.

Measures

Odor identification was measured as a sum of the number of correctly identified odors; the possible range was 0 to 14. Sums were dichotomized to low performance (0–12) and high performance) 13–14, based on their distribution. *Odor threshold* was measured as the level of odor intensity at which the odor could be correctly distinguished from the blanks. Scores could range from 16 (identification at the most dilute level) to 0 (failure to identify the odor even at the most concentrated level). The results from each of the three odor threshold trials were averaged to create a single odor threshold mean and standard deviation value for each participant. Each of the three individual trials was then compared to the mean of the three trials. If any of the three trials were more than one standard deviation above or below the mean of the three trials, that individual value was determined to be an outlier and was set to missing. The remaining values were then averaged to create a single odor threshold value for each participant to use in analyses.

Lifetime pesticide exposure measures were constructed to verify the study design's assumption of greater pesticide exposure among farmworkers than non-farmworkers. This measure was based on items selected from the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards).¹⁸ Participants were asked about 13 residential and occupational pesticide exposures (e.g., residence located within ¼ mile of farm fields, different types of pesticides used in residence, employment as pesticide applicator, employment in farming and other pesticide-exposing industries) for up to 7 age periods (0 to 17 years, 18 to 25 years, 26 to 35 years, 36 to 45 years, 46 to 55 years, 56 to 65 years, 66 years or older). The positive responses were given a value of 1 and were

summed, providing a measure with the values 0 to 13 for each age period. *Lifetime exposure* was the sum of age period specific exposures, without accounting for age, and had possible values 0 to 91. *Index of exposure sources* was lifetime exposure divided by age.

Occupational exposure was obtained by summing the years individuals reported that they had jobs in which they mixed, applied, or were exposed in some other way to pesticides, without accounting for age. These sums were also adjusted for age by dividing exposure years by age.

Participant characteristics included *age* (<30 years, 30 to 34 years, 35 to 44 years, 45 years and older), *education* (0 to 6 grades, 7 to 11 grades, 12 grades or more), *country of birth* (Mexico; US, including Puerto Rico; Central America, Other); *dominant language* (Spanish, English, Other); and *industry of current primary job* (farming, construction, production, food preparation/restaurant, maintenance/cleaning, sales, transportation/truck driver, mechanic, other, unemployed). *Smoking status* was measured with a series of questions about cigarette smoking. Participants who reported any cigarette smoking in the past month were defined as smokers.

Data Analysis

Frequencies and percentages were calculated for participant characteristics of interest and Chi-Square or Fisher's Exact tests were used to test for associations between participant characteristics and farmworker status. Means and standard deviations were derived for the lifetime exposure summary measures and non-parametric Wilcoxon rank-sum tests were used to test the difference between farmworkers and non-farmworkers within each lifetime exposure measure. Chi-Square tests were performed to test the association between the dichotomous high/low odor identification variable and farmworker status, age, sex, and current smoking status. Next, a multivariate logistic regression model was used to examine the relationship between the dichotomous odor identification variable and farmworker status, adjusting for age, sex, and smoking status. Finally, the relationship between farmworker status, age, sex, and smoking status in relation to the odor threshold variable was assessed using t-tests or one-way ANOVAs for bivariate analyses, and also combined into a multivariate linear regression model.

Sensitivity analyses were performed, substituting the lifetime pesticide exposure measure for the farmworker/nonfarmworker variable in the multivariate analyses. Results of these sensitivity analyses were the same as those using the farmworker/nonfarmworker variable.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), and p-values of less than 0.05 were considered statistically significant.

Results

The sample consisted of 551 workers, 304 of whom were farmworkers (Table 1). The sample was largely male, with more males among farmworkers than non-farmworkers (89.8% vs. 77.7%). Farmworkers, as a group were slightly younger and had lower educational attainment than non-farmworkers. A higher percentage of farmworkers were born in Mexico (98.7% vs. 66.0%). Dominant language was Spanish in both groups, with a

greater percentage of farmworkers choosing Spanish (98.4% vs. 91.9%). Non-farmworkers reported currently working in a wide variety of industries, but over half reported their current primary job to be in construction (31.6%) or production (21.5%).

The number of self-reported pesticide exposure sources was significantly greater among farmworkers than non-farmworker for combined occupational and residential exposures with and without adjusting for age (Table 2). Similar measures for occupational exposure were also significantly greater among farmworkers.

Odor identification scores ranged from 2 odors correctly identified to 14; the median score was 13, with 261 individuals overall having a perfect score and 424 (77.2%) correctly identifying 13 or 14 odors. In bivariate analyses, odor identification performance did not differ by farmworker status, sex, or smoking status (Table 3). Older age was associated with poorer odor identification performance ($p=.0007$). These associations remained in multivariate analysis. The odds of identifying 13 or 14 odors correctly for those less than 30 years of age was 1.93 (CI 1.05, 3.55) times the odds of correctly identifying 13 or 14 odors for the 35–44 year old age group, and 2.70 (CI 1.43, 5.09) times the odds of correctly identifying 13 or 14 odors for the 45+ year old age group.

Odor threshold scores varied from 16, a perfect score, to 0, a score indicating that the odor could not be detected at the highest concentration presented. The mean threshold was 6.56 (± 3.24). In bivariate analyses, farmworkers had significantly poorer performance on the odor threshold task ($p<.0001$) than non-farmworkers (Table 4). Performance was also significantly poorer among older participants ($p=0.0049$) and males ($p=0.0007$). These associations remained in multivariate analysis.

Discussion

This study was designed to compare a population of workers with significant current exposure to pesticides with a worker population screened to ensure no current occupational exposure. An established instrument¹⁸ demonstrated that the farmworker sample also reported significantly greater lifetime exposure to pesticides. More detailed analyses of these lifetime exposure data have been presented earlier.¹⁹ Recent exposure is supported by analyses of cholinesterase depression in the same two samples.²⁰

As expected, olfactory performance declined with age for both odor identification and odor threshold tasks; males had poorer performance than females on the odor threshold test. Farmworkers had significantly poorer performance on the odor threshold task than non-farmworkers, with scores averaging almost 1.5 points lower.

Existing studies consistently show declines of olfactory function with age. This may be the result of chronic disease, dental problems, use of medication or other factors associated with aging.²¹ Suggestive evidence exists that olfactory thresholds have a greater age-related response than odor identification and odor discrimination (not tested here).²² In this study, greater age was associated with poorer olfactory function for both odor identification and odor threshold, and these differences persisted in multivariate analysis.

Previous research has shown that gender differences in olfactory function vary by task. While females generally outperform males on tasks like odor identification that require higher cognitive processing,²³ they show similar levels of odor sensitivity if odors are presented in a single session.²⁴ However, females show rapid improvement in sensitivity to odors compared to men when odors are repeated, as in the present study's odor threshold test, a phenomenon that may be linked to hormonal or cognitive factors.²⁴ The present study showed no gender difference in odor identification, but females outperformed males by 1.5 points on odor threshold and this difference remained significant in multivariate analysis.

The olfactory differences observed between farmworkers and non-farmworkers are consistent with the hypothesized effects of pesticide exposure. It is possible that the impaired olfactory function is non-neurologic, perhaps reflecting epithelial damage or irritation due to dust or other chemicals present in the farm environment.²⁵ However, the non-farmworker sample was employed in manual labor occupations in industries such as construction, cleaning and maintenance, and production, which could also have significant exposure to airborne particulates and chemicals. In addition, it would be expected that epithelial damage due to dust would have similar effects on odor identification.

Few studies have examined pesticide exposure and olfactory function. One case study in humans details anosmia following exposure to a pyrethrin-based pesticide.²⁶ Recent research on honeybees and fish has implicated sublethal doses of pesticides in olfactory impairment.^{27,28} Much larger groups of studies have implicated pesticides in neurodegenerative diseases^{5,29–32} and identified loss of olfactory function as an early and common symptom of these diseases.^{15,33} Doty makes clear that such olfactory loss is common across multiple measures of olfaction.³³ Recent reviews of pesticides as etiological factors for neurodegenerative diseases, including Parkinson's disease, conclude that the associations of pesticides with such diseases is likely due to frequent, sub-toxic exposure to multiple pesticides²⁹ and that the development of disease may be complicated by pesticide-gene interactions.³⁴

It is not clear why significant differences were found in odor threshold, but not odor identification. Doty³³ argues that both of these tasks require both the detection and memory of odors, meaning that they are not indicating only impairment of peripheral (e.g., epithelial) function, but rather of the olfactory bulb and olfactory cortex. These results might have differed if the odorant concentrations in the odor identification test were at different levels. Based on research conducted with environmental manganese that showed both peripheral and central olfactory function loss with exposure, we would expect that more detailed examination of olfactory function with pesticides would show similar impairments.³⁵ Of note, chronic manganese exposure is known to cause parkinsonism.

Loss of olfactory function has been recognized for its diagnostic significance for complex diseases. Recent research has used poor olfactory function and other risk factors to develop algorithms capable of distinguishing Parkinson's disease patients from controls, suggesting its importance for early diagnosis.^{36,37}

These results should be interpreted in light of study limitations. This study was conducted among immigrant workers in one region. The farmworker and non-farmworker populations in other parts of the country may experience different current and lifetime exposures. Pesticide exposure was not measured directly; because of the non-persistent nature of most pesticides and their episodic application, measuring exposure precisely is a difficult and expensive task with high subject burden. It was not possible to blind data collectors to study participant group, though they were largely unaware of the study hypothesis. More detailed olfactory, as well as neurological testing was not included in the study.

Despite these limitations, the study has significant strengths. Both the lifetime exposure and olfactory function measures are established and appropriate data collection procedures. Data collectors underwent rigorous training and testing. The study design is robust, with inclusion and exclusion criteria to create groups likely to differ on pesticide exposure, but to be similar in socioeconomic status and racial/ethnic background, factors that might affect odor function and test performance.

Conclusions

Large amounts of pesticides are used in commercial agriculture in the US and elsewhere. Because many pesticides are neurotoxic, workers are at significant risk for neurological consequences. Migrant farmworkers are at risk of long term, low level exposure. However, they are difficult to track to assess the long term neurological sequelae. This study provides suggestive evidence that farmworkers, who have current and lifetime exposures that far exceed those of comparable manual laborers, show subclinical signs of neurological damage. Further research into neurological processes involved with the observed group differences is needed before olfactory function can be used confidently as a marker of neurological risk for this vulnerable population.

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Table 1
Description of the sample, Latino farmworkers and non-farmworkers, North Carolina, 2012.

Participant Characteristics	Farmworkers n=304		Non-farmworkers n=247		p-value ^a
	n	%	n	%	
Gender					0.0001
Male	273	89.8	192	77.7	
Female	31	10.2	55	22.3	
Age					0.0565
< 30 years	73	24.0	45	18.2	
30–34 years	83	27.3	53	21.5	
35–44 years	88	28.9	86	34.8	
45+ years	60	19.7	63	25.5	
Education ^b					<.0001
0–6 grade	118	38.9	80	32.5	
7–11 grade	148	48.8	79	32.1	
12 grade or more	37	12.2	87	35.4	
Country of Birth					<.0001
Mexico	300	98.7	163	66.0	
United States/Puerto Rico	1	0.3	17	6.9	
Central America	3	1.0	52	21.1	
Other	–	–	15	6.1	
Preferred Language					<.0001
Spanish	299	98.4	227	91.9	
English	2	0.7	19	7.7	
Other	3	1.0	1	0.4	
Industry of Current Job					NA
Agriculture	304	100	–	–	
Construction	–	–	78	31.6	
Production	–	–	53	21.5	
Food preparation/restaurant	–	–	22	8.9	

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Participant Characteristics	Farmworkers n=304		Non-farmworkers n=247		p-value ^a
	n	%	n	%	
Maintenance/cleaning	–	–	17	6.9	
Sales	–	–	15	6.1	
Transportation/truck driver	–	–	11	4.4	
Mechanic	–	–	9	3.6	
Other	–	–	10	4.0	
Unemployed	–	–	32	13.0	

^aBased on Chi-Square or Fisher's Exact test, as appropriate

^bMissing 2 observations

Table 2

Comparison of lifetime exposure to occupational and residential pesticide sources: Latino farmworkers (n=304) and non-farmworkers (n=247), North Carolina, 2012.

	Farmworkers		Non-Farmworkers		p-value
	Mean	SD	Mean	SD	
Total Exposure					
Lifetime exposure ^a	12.00	5.44	5.48	4.03	p<0.001
Index of exposure sources ^b	0.34	0.12	0.14	0.10	p<0.001
Occupational Exposure					
Total years in pesticide-exposing jobs	13.11	8.15	3.84	5.78	p<0.001
Total years in pesticide-exposing job/age	0.36	0.18	0.09	0.13	p<0.001

^aSum of age period-specific exposures (possible value range 0-91)

^bSum of age period-specific exposures/age

Table 3

Bivariate and multivariate analysis results comparing odor identification performance of Latino farmworkers and non-farmworkers. N=549. North Carolina, 2012.

Variable	Bivariate Analysis		p-value ^a	Multivariate Logistic Regression OR (95% CI)
	Odor ID Score < 13 N (row %)	Odor ID Score ≥ 13 N (row %)		
Farmworker status			0.8033	
Farmworker	68 (22.4)	236 (77.6)		REF
Non-farmworker	57 (23.3)	188 (76.7)		1.01 (0.67, 1.54)
Age			0.0007	
<30 years	18 (15.3)	100 (84.8)		REF
30–34 years	21 (15.4)	115 (84.6)		1.02 (0.51, 2.02)
35–44 years	45 (26.0)	128 (74.0)		0.52 (0.28, 0.95)
45+ years	41 (33.6)	81 (66.4)		0.37(0.20, 0.70)
Sex			0.1996	
Female	15 (17.4)	71 (82.6)		REF
Male	110 (23.8)	353 (76.2)		0.72 (0.38, 1.33)
Current smoking status			0.7229	
Smoker	27 (21.6)	98 (78.4)		REF
Non-smoker	98 (23.1)	326 (76.9)		0.94 (0.57, 1.56)

^a Chi-Square test

Table 4

Bivariate and multivariate analysis results comparing odor threshold performance of farmworkers and non-farmworkers. N=551. North Carolina, 2012.

Variable	Bivariate Analysis		Multivariate Linear Regression	
	Odor Threshold Mean (SD)	p-value ^a	Odor Threshold Least Square Means (SE)	p-value
Farmworker status		<.0001		<.0001
Farmworker	5.91 (2.88)		6.36 (0.25)	
Non-farmworker	7.35 (3.48)		7.80 (0.26)	
Age		0.0049		0.0021
<30 years	7.44 (3.30)		7.95 (0.32)	
30–34 years	6.50 (3.08)		7.10 (0.32)	
35–44 years	6.39 (3.37)		6.78 (0.29)	
45+ years	6.01 (3.01)		6.49 (0.34)	
Sex		0.0007		0.0048
Female	7.82 (3.76)		7.61 (0.37)	
Male	6.32 (3.08)		6.54 (0.17)	
Current smoking status		0.5015		0.6108
Smoker	6.38 (2.94)		7.16 (0.33)	
Non-smoker	6.61 (3.32)		7.00 (0.19)	

^a t-test or one-way ANOVA